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The metabolic syndrome, atherosclerosis and cognitive functioning in a non-demented population: The Hoorn Study

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ABSTRACT

Background: The metabolic syndrome (MetS) is associated with cognitive deficits and atherosclerotic vascular disease. We examined whether the relation between the MetS and cognitive dysfunction is mediated by measures of atherosclerosis or the presence of clinically manifest cardiovascular disease.
Methods: In 380 individuals (153 with MetS; 60–87 years) from the population based Hoorn Study, measures of atherosclerosis including carotid intima-media thickness (c-IMT), flow mediated dilation (FMD), ankle-brachial index and the presence of clinically manifest cardiovascular disease were assessed at baseline and 7 later years at follow-up. Cognitive functioning (information processing speed, memory, and attention and executive functioning) was assessed at follow-up. The relation between the MetS, atherosclerosis and cognitive functioning was assessed with linear regression analysis.
Results: Individuals with MetS showed worse performance on information processing speed (adjusted mean difference *z*-score ± SE: −0.22 ± 0.6; $p = 0.01$) and attention and executive functioning (−0.32 ± 0.07; $p < 0.001$), but not on the domain memory. The affected cognitive domains were also associated with measures of atherosclerosis (standardised B (95%CI) c-IMT: −0.14 (−0.24; −0.05); $p < 0.01$; FMD: 0.13 (0.02; 0.24), $p < 0.05$) and a history of clinically manifest cardiovascular disease: (−0.29 (−0.47; −0.11); $p < 0.01$). However, the relation between the MetS and cognitive functioning did not change after adjustment for c-IMT, FMD or a history of clinically manifest cardiovascular disease ($p > 0.05$).
Conclusion: In this population based cohort, the relation between the MetS and cognitive dysfunction was not mediated by atherosclerosis or a history of cardiovascular disease. These findings should stimulate future studies to elucidate alternative mechanisms underlying cognitive deficits in individuals with MetS.

1. Introduction

The clustering of cardiovascular risk factors, often referred to as the metabolic syndrome (MetS), is associated with cognitive decrements and the development of dementia [1,2]. This relation may be mediated by atherosclerotic vascular disease.

Individuals with MetS are at increased risk for carotid atherosclerosis, endothelial dysfunction, ischemic heart disease and cerebrovascular disease [3–5]. Atherosclerotic vascular disease may in turn affect the brain, not only by increasing the risk of thromboembolic stroke [6], but possibly also by affecting cerebral perfusion, leading to malfunction and degeneration of neuronal cells [7].

Large population-based studies have demonstrated a link between indices of atherosclerosis and cognitive dysfunction or dementia [8]. Affected cognitive domains include memory, information processing speed, and executive functioning [9,10], a cognitive profile which is similar to the one observed in individuals with the MetS [11]. Also in individuals without clinically manifest cardiovascular disease, carotid intima media thickness predicted subsequent cognitive decline [12].

Although atherosclerosis has often been considered to mediate the relation between the MetS and cognitive decline, this mediating effect has not yet been studied in sufficient detail. The present study therefore examined the relation between the MetS, atherosclerosis and cognitive functioning in a population of non-demented

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older individuals. Presence of the MetS and several measures of atherosclerosis were related to a detailed cognitive assessment 7 years later.

2. Methods

2.1. Study population

The Hoorn study is a population-based study on glucose metabolism and cardiovascular risk in the general population. The population and study design have been described earlier [13]. The study started in 1989 and included 2484 randomly selected Caucasian participants aged 50–75 years from the middle-sized Dutch town of Hoorn (T1). In 1996–1998 (T2), all surviving participants ($n = 2086$) were invited for a second examination, to which 1513 agreed [14]. In the 2000–2001 follow-up examination (T3), 1074 individuals of the Hoorn study cohort, including all those who were diagnosed as having type 2 diabetes ($n = 176$), and random samples of individuals with normal ($n = 705$) and impaired ($n = 193$) glucose metabolism, were invited, of whom 647 (60%) agreed to participate [15]. In 2005–2008 (T4) all independently living participants ($n = 549$) were reinvited, to which 385 (70%) agreed to participate.

Cognitive functioning was only assessed at the 2005–2008 examination. None of the participants had cognitive disturbances interfering with functional independence at the moment of cognitive testing. For the present study we excluded participants with an unreliable assessment of cognitive functioning (e.g. deafness, language difficulties; $n = 5$), leaving 380 participants for the present analyses. In the present paper, the 2000–2001 examination will be referred to as baseline, and the 2005–2008 examination as follow-up.

Because we were interested in the possible causal relationship between the MetS, atherosclerosis and late life cognitive dysfunction, we defined the MetS and measures of atherosclerosis at baseline, 7 years prior to cognitive testing. In secondary analyses we evaluated the mediating effect of the progression of atherosclerosis over 7 years on the relation between the MetS at baseline and cognitive functioning at follow-up.

The local ethics committee approved the study and written informed consent was obtained from all participants.

2.2. The metabolic syndrome

The metabolic syndrome was defined as having three or more of the following criteria at baseline: waist circumference >88 cm for women and >102 cm for men; triglycerides $\geq$1.7 mmol/l; HDL cholesterol <1.3 mmol/l for women and <1.0 mmol/l for men; blood pressure $\geq$130/85 mm Hg (or antihypertensive medication), and fasting blood glucose $\geq$6.1 mmol/l (ATP-III) (NCEP JAMA 2001). Since information on 2-h postload glucose was also recorded in this population, the glucose criterion was slightly modified and was also considered fulfilled when the 2-h glucose concentration was $\geq$7.8 mmol/l [16].

2.3. Measures of atherosclerosis

2.3.1. Carotid intima-media thickness (c-IMT)

Ultrasound assessment of the c-IMT was performed at baseline and follow-up. Procedures and reproducibility of scanning are described in detail elsewhere [15]. In summary, an ultrasound scanner (350 Series; Pie Medical, Maastricht, The Netherlands), equipped with a 7.5-MHz linear probe, was operated by a single observer. Three measurements, 4 s each, were performed in the right common carotid artery at 10 mm proximal to the carotid bulb. The mean of these three measurements was calculated and included in the analysis. Images were registered and analysed by a computer equipped with vessel wall movement detection software and an acquisition system (Wall Track System; Pie Medical).

2.3.2. Endothelial function

Endothelium-dependent flow-mediated dilation (FMD) of the right brachial artery was assessed at baseline. The measurement protocol has been described in detail [3]. Briefly, baseline diameter (mean of three measurements) and peak flow velocity (mean of two measurements) were determined. A pressure cuff, placed on the forearm, was then automatically inflated and kept constant at supra-systolic pressure (brachial systolic pressure + 100 mmHg) in order to induce forearm ischemia. After 5 min the cuff was released, which is followed by an increase in blood flow. This increase in blood flow increases shear stress, which serves as the stimulus for FMD. After cuff release, the diameter was measured at 45, 90, 180 and 300 s. The maximum diameter in any of these four measurements was used in the statistical analysis. In addition, non-endothelium dependent nitroglycerin-mediated dilation (NMD) was determined, which served as a control condition for FMD. NMD was calculated as the percentage change in arterial diameter from baseline to 5 min after administration of 400 μg sublingual nitroglycerin [3].

2.3.3. Clinically manifest cardiovascular disease

Peripheral vascular disease, ischemic heart disease and history of stroke were assessed at baseline and follow-up. Peripheral vascular disease was defined as intermittent claudication assessed with the Rose questionnaire, Ankle Brachial Index $\leq$0.9, history of surgery or endovascular treatment for arterial disease, or lower limb amputation. Ischemic heart disease was defined as Minnesota Code 1.1–1.3, 4.1–4.3, 5.1–5.3, or 7.1 on the electrocardiogram or self-reported history of myocardial infarction. A history of stroke was based on self-report. Any cardiovascular disease was defined as peripheral vascular disease, ischemic heart disease or history of stroke.

2.4. Cognitive assessment

An extensive standardised neuropsychological test battery was obtained at the follow-up examination, including twelve verbal and non-verbal tasks, administered in a fixed order. The tasks were divided into six cognitive domains. This division was made a priori, according to standard neuropsychological practice and cognitive theory as described in detail by Lezak et al. [17]. For the present study we focused on those cognitive domains which have previously been shown to be particularly affected in individuals with the MetS and individuals with atherosclerosis, namely the domains memory, information processing speed and attention and executive functioning [9,11]. The domain *memory* included tests for four subdomains: 'working memory' assessed by the forward and backward digit span of the Wechsler Adult Intelligence Scale-III (WAIS-III) and the Corsi Block-Tapping Task; 'immediate memory and learning rate', including verbal memory assessed by the Rey Auditory Verbal Learning Test and visual memory assessed by the Location Learning Test; 'forgetting rate' assessed by the delayed recall of the Rey Auditory Verbal Learning Test and of the Location Learning Test; and 'incidental memory' assessed by the delayed trial of the modified Rey Complex Figure. The domain *information processing speed* was assessed by the Trail Making Test Part A, the Stroop Color-Word Test (Parts I and II), and the subtest Digit Symbol of the WAIS-III. The domain *attention and executive function* was assessed by the Trail Making Test Part B, the Stroop Color-Word Test (Part III), the Brixton Spatial Anticipation Test, a letter fluency test using the 'N' and 'A', and category fluency using animal names.

Raw test scores were standardised into *z*-scores. One *z*-score was derived for each domain by averaging tests comprising that domain.

Pre-morbid IQ was estimated with the Dutch version of the National Adult Reading Test. Depressive symptoms were assessed with the validated Dutch version of the 20-item Centre for Epidemiologic Studies Depression Scale (CES-D). The proportion of persons scoring ≥16 (indicating possible depression) was recorded.

2.5. Other measurements

Systolic and diastolic blood pressure, body mass index (BMI), waist-to-hip ratio, fasting glucose concentration, 2-h postload glucose concentration, HbA1c levels, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, were determined as described elsewhere [13]. The presence of diabetes was determined based on WHO criteria (WHO 1999). Self-reported information on the participants' current use of medications, medical history and current smoking status (yes/no) was obtained by a standardised questionnaire.

2.6. Statistical analysis

Demographic variables, vascular and metabolic risk factors levels, and measures of atherosclerosis were compared between participants with and without MetS with independent *T*-test for continuous variables and chi-square test for proportions.

To answer the question whether the relation between the MetS and cognitive dysfunction is mediated by measures of atherosclerosis we first assessed the associations between the MetS and cognition, between the MetS and atherosclerosis, and between atherosclerosis and cognition with linear regression analyses, adjusted for age and sex, and cognition also for estimated IQ. The cognitive domains on which the MetS group performed worse than the noMetS group and the measures of atherosclerosis that were significantly related to cognitive performance were considered in the mediation analyses.

The possible mediating effect of atherosclerosis on the relation between the MetS and cognitive performance was assessed in a stepwise linear regression analysis in which we adjusted the difference in cognitive performance between the noMetS and MetS group for measures of atherosclerosis at baseline. The change in between-group difference before and after adjustment for the mediator (atherosclerosis) was assessed. In addition, we estimated the corresponding 95% confidence interval (CI) with a bootstrapping technique [18]. Bootstrapping is a computer-based method that involves repeated sampling from the data and estimation of the mediating effect in each resampled data set. By repeating this process thousands of times, an empirical approximation of the sampling distribution is built and used to reconstruct the 95% CI. The mediating effect is said to be present if the 95% CI does not contain zero. We computed bootstrapped (bias-corrected) confidence intervals (5000 samples) for the size of the specific mediating 'effects' using SPPS macros provided by Preacher & Hayes [18].

In secondary models, alternative mediators of the relation between MetS and cognition were addressed. To prevent multicollinearity this was done in six separate models for each individual risk factor of the MetS (hypertension, hyperglycemia, dyslipidemia, central obesity), current smoking, and possible depression. Because the study population was enriched for type 2 diabetes, which is a risk factor for cognitive decrements and atherosclerosis, we also reanalysed the data after excluding all participants with type 2 diabetes.

Finally, we evaluated whether the progression of atherosclerotic measures between baseline and follow-up mediates the relation between the MetS and cognition by repeating step 1 and 2 for measures of atherosclerosis assessed at follow-up, adjusted for the baseline measurement.

Table 1
Characteristics of the study population at baseline.

	No MetS (n = 227)	MetS (n = 153)	p-Value
Age, years	67.8 ± 5.5	67.7 ± 5.4	n.s.
Sex (% male)	52%	48%	n.s.
Estimated IQ[a]	98 ± 12	97 ± 14	n.s.
Systolic blood pressure (mmHg)	134 ± 18	147 ± 18	<0.001
Diastolic blood pressure (mmHg)	79 ± 11	87 ± 10	<0.001
Antihypertensive medication	22%	49%	<0.001
BMI (kg/m^2)	25.7 ± 2.7	29.6 ± 3.7	<0.001
Waist–hip ratio	0.90 ± 0.09	0.96 ± 0.09	<0.001
Total cholesterol (mmol/l)	5.7 ± 1.0	5.7 ± 1.1	n.s.
HDL-cholesterol (mmol/l)	1.5 ± 0.4	1.2 ± 0.4	<0.001
LDL-cholesterol (mmol/l)	3.6 ± 0.9	3.6 ± 0.9	n.s.
Triglycerides (mmol/l)	1.2 ± 0.4	2.0 ± 1.0	<0.001
Cholesterol lowering drugs	14%	22%	0.045
Fasting glucose (mmol/l)	5.7 ± 0.9	6.6 ± 1.4	<0.001
2-h post-load glucose (mmol/l)	6.3 ± 2.1	8.3 ± 2.7	<0.001
HbA1c (%)	5.8 ± 0.5	6.2 ± 0.8	<0.001
Diabetes	7%	31%	<0.001
Current smoking	13%	9%	n.s.

Data are presented as mean ± SD or *n* (%).
[a] Assessed at follow-up.

3. Results

Table 1 shows the baseline characteristics of the participants with and without MetS. Groups did not differ in age, sex or estimated IQ. Of the 153 participants with the MetS, 120 (78%) scored above the cut-off for waist circumference, 93 (61%) for triglyceride levels, 73 (48%) for HDL levels, 143 (94%) for blood pressure levels, and 120 (78%) for glucose levels. The raw cognitive test scores of both groups are presented in Table 2.

3.1. The MetS and atherosclerosis at baseline and cognitive functioning at follow-up

Individuals with the MetS had a greater c-IMT, worse endothelial function, reflected by a lower FMD and similar NMD, and a higher prevalence of ischemic heart disease at baseline than individuals without the MetS (Table 3). Regarding cognition, individuals with the MetS showed worse performance at follow-up on the domain information processing speed (adjusted mean *z*-score ± SE noMetS: 0.09 ± 0.5, MetS: −0.13 ± 0.06; $p = 0.01$) and attention and executive functioning (noMetS: 0.13 ± 0.06, MetS: −0.19 ± 0.07; $p < 0.001$). No significant difference in memory performance was observed (Table 4).

The relation between markers of atherosclerosis at baseline and cognitive functioning at follow-up in the whole population is shown in Table 5. An increased c-IMT was associated with worse information processing speed (standardised B (95%CI): −0.14(−0.24; −0.05); $p = 0.004$) and attention and executive functioning (−0.11 (−0.21; −0.01); $p = 0.04$). Decreased FMD was associated with worse attention and executive functioning (standardised B (95%CI): 0.13 (0.02; 0.24), $p = 0.02$). The presence of ischemic heart disease or any CVD was associated with worse information processing speed (B (95% CI) ischemic heart disease: −0.21(−0.40; −0.02), $p = 0.03$; any CVD: −0.29 (−0.47;

Table 2
Raw cognitive test scores.

	Range of scores	Controls (n = 227)	MetS (n = 153)
Information processing speed			
Trail making test part A (s)[a]	20–161	49.3 ± 19.9	51.5 ± 21.9
Stroop color word test I (s)[a]	32–133	47.9 ± 8.0	49.9 ± 11.6
Stroop color word test II (s)[a]	39–137	63.6 ± 11.8	66.1 ± 16.0
Symbol substitution test	18–94	52.4 ± 14.5	49.7 ± 14.4
Attention and executive functioning			
Trail making test part B (s)[a]	41–407	121.3 ± 62.3	139.8 ± 69.9
Stroop color word test III (s)[a]	50–467	125.2 ± 46.4	137.9 ± 58.3
Brixton spatial anticipation test (errors)[a]	7–47	20.7 ± 7.4	21.9 ± 6.9
Letter fluency (mean N + Á)	2–24	11.0 ± 4.2	10.1 ± 4.0
Category fluency (No. of animals)	8–63	30.8 ± 8.4	30.3 ± 9.0
Memory			
Working memory			
WAIS-II digit span forward (productscore)	12–126	45.1 ± 17.9	44.8 ± 19.7
WAIS-II digit span backward (productscore)	4–104	25.0 ± 15.9	21.6 ± 13.2
Corsi Block-Tapping test forward (productscore)	9–96	38.5 ± 12.2	36.5 ± 12.7
Corsi Block-Tapping test backward (productscore)	2–88	34.7 ± 15.5	34.4 ± 15.9
Immediate memory and learning rate			
RALVT total trials 1–5 (words)	5–61	36.2 ± 10.4	35.4 ± 9.9
LLT total trials 1–5 (errors)[a]	0–163	34.2 ± 26.2	29.8 ± 23.2
Forgetting rate			
RAVLT delay (words)	0–15	6.8 ± 3.4	6.8 ± 3.0
LLT delay (errors)[a]	0–33	4.3 ± 5.9	3.3 ± 4.3
RAVLT recognition (words)	0–30	27.6 ± 3.0	27.8 ± 3.2
Incidental memory			
Rey Complex Figure Test delay (points)	0–30	14.2 ± 6.3	14.2 ± 6.3

RAVLT: Rey auditory verbal learning test; LLT: location learning test. Raw test scores per group are represented as mean ± SD. Higher scores indicate better performance except when indicated.

[a] Higher scores indicate poorer performance.

Table 3
Between-group differences in measures of atherosclerosis at baseline.

	No MetS (n = 227)	MetS (n = 153)	p-Value
c-IMT, mm	0.83 ± 0.17	0.88 ± 0.15	0.01
Endothelial dependent FMD[a], %	4.7 ± 3.8	3.7 ± 3.1	0.02
Non-endothelial dependent NMD[b], %	10.7 ± 5.4	9.9 ± 5.8	0.21
		Clinically manifest CVD	
Peripheral vascular disease[c]	33 (15%)	25 (17%)	0.61
Ischemic heart disease[d]	77 (34%)	65 (43%)	0.09
History of stroke	19 (8%)	10 (7%)	0.50
Any CVD[e]	111 (49%)	79 (52%)	0.60

[a] Flow mediated (endothelial dependent) dilation of the brachial artery.
[b] Nitroglycerin mediated (endothelial independent) dilation of the brachial artery.
[c] Rose questionnaire: intermittent claudication, ABI < 0.9, arterial operation or amputation.
[d] Self reported history of myocardial infarction or ischemic heart disease on ECG.
[e] History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke.

−0.11), p = 0.002). A trend was observed between a history of stroke at baseline and worse performance on the domain information processing speed (−0.56 (−1.15; 0.025); p = 0.06) and memory (−0.63 (−1.26; 0.01); p = 0.05).

Table 4
Group differences in cognitive performance at follow-up.

	No MetS (n = 227)	MetS (n = 153)	p-Value
Info processing speed	0.09 ± 0.05	−0.13 ± 0.06	0.01
Attention and executive functioning	0.13 ± 0.06	−0.19 ± 0.07	<0.001
Memory	−0.06 ± 0.06	0.09 ± 0.07	n.s.

Data are presented as mean standardised z-scores ± SE adjusted for age, sex and estimated IQ.

3.2. Mediation of the association between the MetS and cognition by baseline atherosclerosis

As can be seen from Table 6, the mean difference in information processing speed between the MetS and noMetS group did not notably change after additional adjustment for c-IMT, FMD and any CVD at baseline (change in between-group difference final model: 0.03). The corresponding 95%CI estimated with the bootstrap method (−0.06; 0.05) indicated that these measures of atherosclerosis did not significantly mediate the association between MetS and cognition, because the 95%CIs contain zero and are relatively narrow. Also the mean group difference in attention and executive functioning did not change after adjustment for atherosclerosis at baseline (change in between-group difference final model (bootstrap 95%CI): 0.01 (−0.07; 0.01)). Further adjustment for current smoking, and possible depression did not alter the results (data not shown). Of the five individual risk factors of the MetS, only hyperglycemia slightly mediated the relation between the MetS and information processing speed (−0.10 (−0.22; −0.003)), but not between MetS and attention and executive functioning (−0.06 (−0.16; 0.05)).

3.3. The association between the MetS, baseline atherosclerosis and cognition in individuals without type 2 diabetes

After exclusion of all individuals with type 2 diabetes (n = 64), the noMetS group included 211 individuals and the MetS group 105 (mean age 67.7 ± 5.6 and 67.5 ± 5.2, respectively). The between-group differences in measures of atherosclerosis, cognitive functioning and the relation between measures of atherosclerosis at baseline and cognition at follow-up were similar to the values from the analyses that included the patients with type 2 diabetes, as shown in Tables 3–5 (supplementary material online). Only the difference in endothelial dependent FMD between the MetS and noMets group became smaller and non-significant (noMetS: 4.8 ± 3.8, MetS: 4.2 ± 3.4). Similar to the results shown in Table 6, the group difference in information processing speed

Table 5
Relation between measures of atherosclerosis at baseline and cognition at follow-up in the whole study sample ($n = 380$).

	Information processing speed	Attention and executive functioning	Memory
c-IMT, mm	−0.14 (−0.24; −0.05)**	−0.11 (−0.21; −0.01)*	−0.10 (−0.21; 0.002)
Endothelial dependent FMD[a,f], %	0.05 (−0.05; 0.16)	0.13 (0.02; 0.24)*	−0.02 (−0.13; 0.09)
Non-endothelial dependent NMD[b,f], %	0.05 (−0.05; 0.16)	0.01 (−0.04; 0.18)	0.10 (−0.02; 0.21)
Clinically manifest CVD			
Peripheral vascular disease[c]	−0.21 (−0.46; 0.05)	0.03 (−0.24; 0.30)	−0.25 (−0.52; 0.02)
Ischemic heart disease[d]	−0.21 (−0.40; −0.02)*	0.07 (−0.14; 0.27)	−0.01 (−0.22; 0.19)
History of stroke	−0.56 (−1.15; 0.03)	−0.22 (−0.85; 0.41)	−0.63 (−1.26; 0.01)
Any CVD[e]	−0.32 (−0.49; −0.14)**	0.07 (−0.13; 0.26)	−0.16 (−0.35; 0.04)

Regression coefficients indicate the change in *z*-score per SD for continuous variables and per category (no/yes) for dichotomous variables, adjusted for age and sex.
[a] Flow mediated dilation of the brachial artery.
[b] Nitroglycerin mediated dilation of the brachial artery.
[c] Rose questionnaire: claudicatio, ABI <0.9, arterial operation or amputation.
[d] Self reported history of myocardial infarction or ischemic heart disease on ECG.
[e] History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke.
[f] Lower values reflect worse function.
* $p < 0.05$.
** $p < 0.01$.

Table 6
Mean difference in cognitive performance at follow-up between individuals with ($n = 153$) and without ($n = 227$) the MetS adjusted for measures of atherosclerosis at baseline.

	Information processing speed	Attention and executive functioning
Age, sex, estimated IQ	−0.22 (−0.38; −0.05)*	−0.32 (−0.49; −0.14)***
Previous + c-IMT	−0.19 (−0.36; −0.02)*	−0.33 (−0.52; −0.15)***
Previous + endothelial dependent FMD[a]	−0.24 (−0.43; −0.06)*	−0.33 (−0.52; −0.15)***
Previous + any CVD[b]	−0.25 (−0.43; −0.07)**	−0.33 (−0.52; −0.14)***

[a] Flow mediated dilation of the brachial artery.
[b] History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

(-0.27 ± 0.09; $p = 0.003$) and attention and executive functioning (-0.32 ± 0.10; $p = 0.002$) did not change after adjustment for measures of atherosclerosis at baseline (change in between-group difference (bootstrap 95%CI): 0.03 (−0.08; 0.02) and −0.03 (−0.06; 0.02), respectively) (Table 7).

3.4. Mediation of the association between the MetS and cognition by the progression of atherosclerosis between baseline and follow-up

After correction for the baseline measurements of atherosclerosis, there was no association between c-IMT, peripheral vascular disease or ischemic heart disease at follow-up and cognitive functioning at follow-up (all $p > 0.05$). However, incident stroke (stroke between baseline and follow-up) was associated with reduced information processing speed (−0.56 (−0.97; −0.14); $p = 0.01$), but not with attention and executive functioning or memory performance. Incident stroke did not mediate the relation between the MetS and worse performance on information processing speed or attention and executive functioning (change in between-group difference (bootstrap 95%CI): −0.02 (−0.07; 0.01) and −0.005 (−0.03; 0.004)) respectively.

4. Discussion

In the present population-based study both the MetS and markers of atherosclerosis were associated with reduced cognitive functioning, but the relation between the MetS and cognitive decrements was not mediated by measures of atherosclerosis or the presence of clinically manifest cardiovascular disease.

The profile and size of the cognitive decrements we observed in individuals with MetS are in line with previous findings, reflecting mild reductions in information processing speed and attention and executive functioning [1,11]. Problems with memory have also been reported [19]. However, in contrast to our study, previous studies primary assessed immediate verbal memory performance, which strongly depends on attentional capacity, and not so much on the capability to consolidate information. Differences in cognitive performance were mainly observed on tests with a high attentional demand (Table 2), indicating that the cognitive problems in individuals with MetS will become most evident in complex situations, e.g. when two tasks are executed simultaneously. The use of a detailed cognitive assessment allowed us to detect subtle decrements in cognitive functioning before it became clinically manifest. Examining underlying mechanisms of these early stages of cognitive

Table 7
Mean difference in cognitive performance at follow-up between individuals with ($n = 105$) and without ($n = 211$) the MetS and without type 2 diabetes, adjusted for measures of atherosclerosis at baseline.

	Information processing speed	Attention and executive functioning
Age, sex, estimated IQ	−0.27 (−0.45; −0.09)**	−0.32 (−0.52; −0.12)**
Previous + c-IMT	−0.25 (−0.44; −0.07)**	−0.32 (−0.52; −0.12)**
Previous + endothelial dependent FMD[a]	−0.31 (−0.51; −0.12)**	−0.29 (−0.48; −0.09)**
Previous + any CVD[b]	−0.30 (−0.49; −0.11)**	−0.29 (−0.49; −0.09)**

[a] Flow mediated dilation of the brachial artery.
[b] History of peripheral vascular disease, myocardial infarction, ischemic heart disease on ECG, or stroke.
** $p < 0.01$.

dysfunction is relevant, because treatment benefits are expected to be largest when the underlying brain damage is still relatively modest.

Our results on the relation between cognitive performance and measures of carotid atherosclerosis [10,20], endothelial function [20] and clinically manifest cardiovascular disease [9,21] are also in agreement with results from previous population based studies. The important finding of our study is that despite the fact that we confirm that the MetS and atherosclerosis are both associated with impaired cognition, we now clearly demonstrate that atherosclerosis does not modulate the relation between the MetS and cognition. In addition to traditional mediation analyses, we also calculated the respective 95% CI of the mediation effect by using a bootstrapping technique. This technique provides information on the reliability of the point estimates for possible mediation effects. The observed 95% CIs were relatively narrow, indicating that the mediation effect could be reliably estimated in this study sample. Although the modulating role of atherosclerosis on the relation between MetS and cognition had not yet been studied in sufficient detail, it has often been proposed as an important mechanism. Our results however, do not support this hypothesis, indicating that other mechanisms are likely to play a role. For example, etiological factors shared between atherosclerosis and the MetS, such as inflammation, may drive the association with cognition. Chronic inflammation is an important risk factor for atherosclerosis and is linked with the MetS and age-related cognitive decline [11,22]. In addition, each component of the MetS is individually associated with atherosclerosis and reduced cognitive functioning [23]. Previous studies have identified hyperglycemia as the main contributor to deficits in cognitive functioning in individuals with MetS [11,24]. Also in our study hyperglycemia slightly modulated the relation with information processing speed.

The other components of the MetS, including hypertension, adiposity and hypercholesterolemia, did also not mediate the relation between the MetS and cognitive functioning in this study. However, this does not rule out the association between MetS and the development of cognitive dysfunction. Indeed, exposure to vascular risk factors at midlife has shown to be more strongly related to late life cognitive function than exposure to these risk factors during late life [25,26]. The age at which the vascular risk factors are assessed should therefore be considered in interpretation of these results.

Our findings do not exclude that the relation between MetS and cognitive dysfunction is mediated by other manifestations of vascular disease, such as cerebral small vessel disease. Small vessel disease, such as white matter abnormalities and (lacunar) infarcts, is more common in individuals with MetS [24,28,29] and is associated with a similar cognitive profile,including mental slowing and problems with executive functioning [27]. Unfortunately, brain MRI data was not available from our cohort.

To our knowledge, we are the first to examine the impact of atherosclerosis on the association between the MetS and cognitive dysfunction. Strengths of this study are the detailed recording of measures of atherosclerosis over a long follow-up period in a well-defined population-based cohort, as well as the comprehensive assessment of cognitive functioning. However, some measures of cardiovascular disease, such as stroke, were based on self-report. Another limitation is attrition, which can lead to selection bias. Although this is inherent to the longitudinal design and the intensive character of this study, this may have led to an underestimation of the effects because subjects with severe vascular disease or cognitive deficits are more likely to drop out. Indeed, previous reports on the Hoorn study population have shown that cardiovascular mortality was associated with an unfavourable risk factor profile at baseline [30]. Our results apply therefore to the variation in cognitive functioning in a relatively healthy population of older individuals, but cannot be generalised to the risk of developing dementia. Finally, cognition was only assessed once. Therefore we were not able to determine which individuals showed cognitive decline.

Despite these limitations, we still observe an association between the MetS, atherosclerosis and cognition, supporting the notion that also mild forms of atherosclerosis are related to worse cognitive functioning.

5. Conclusion

These results indicate that atherosclerosis or the presence of clinically manifest cardiovascular disease does not account for the observed reductions in cognitive functioning in individuals with the MetS. Whether shared vascular and metabolic risk factors of MetS and atherosclerosis play a role in the development of cognitive deficits remains to be elucidated. Understanding these mechanisms is essential for future intervention studies aiming to reduce the detrimental effect of MetS on the brain.

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Competing interests

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.08.032.

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